THE OHIO JOURNAL OF SCIENCE

VOL. XLIII JANUARY, 1943 No. 1

THE GENETICS OF CONGENITAL PYLORIC STENOSIS

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Congenital pyloric stenosis is a condition which usually becomes manifest about the fourth week after the patient's birth. The symptom of projectile vomiting with constipation and the signs of pyloric tumor and gastric peristalsis are occasioned by anatomical changes which can only be observed if the case is surgically treated or examined at autopsy. The essential feature of the disease, muscular hypertrophy of the pylorus, is a structural change, probably present before birth for it has been identified in a stillborn child and a seven months' foetus (Strachaner 1927). The disease has a low familial incidence and, though several pedigrees have been published which show more than one affected child, the mode of inheritance is uncertain. Cautley and Dent (1902) reported instances of the disease in a great aunt and her nephew and a family with three affected sibs was mentioned by Heubner (1906). There are other early records of more than one case in a family (Freund, 1903, Grissen, 1904, Ashby, 1907, and Rosenhaupt, 1907). Still (1915) pointed out that in a series of 94 cases there were three pairs of affected sibs and Finkelstein (1924) recorded one family with four and another with three sibs affected. A brother and sister, both affected, whose father may also have had pyloric stenosis in infancy, were described by Caulfield (1926), and Ashton (1929) found an authentic example of mother and son both affected. Cockayne (1934) published two pedigrees, each with a pair of first cousin patients. The case of a male patient, whose brother's son and daughter and whose sister's two sons developed the same condition, was reported by Halbertsma (1935). De Lange (1936) put on record a family of a female patient whose sister's twin sons were also patients. Fabricius and Vogt-Moller (1937) described the case of a normal woman who had three affected children by her first husband and four by her second. Four pedigrees were investigated by Cockayne (1938): in one there was an affected pair of second cousins, in two pedigrees there were pairs of first cousin patients and, in the other family, there was a pair of affected first cousins, of whom the mother of one and the sister of the other suffered from vomiting during the first weeks of life.

Evidence in favor of hereditary influence in the causation of the disease has been obtained from the study of twins. Indeed, Ford, Brown and McCreary (1941) consider twining to be unduly frequent among affected cases. When the twins are binovular, it is usually found that if one is affected the other is normal; except in one instance (Sheldon, 1938) monovular twins are equally affected.

When a series of hospital cases of congenital pyloric stenosis is examined with respect to the birth order of the patients, it is regularly found that between 40 and 60 per cent are the result of first pregnancies: for example, Still (1929) found that

48.5 per cent were first born in 400 cases. The inference that primogeniture is a causal factor has been accepted by many authorities (Ford, Ross and Brown 1941) but not all (Bell and Fitsgibbon, 1934). Since the statistical proof is not easy, a further investigation on this point is not, perhaps, out of place. Pearson (1914), for example, asserted that primogeniture was a cause of quite a number of physical and mental defects: in some cases, later investigators have shown that his conclusions cannot be upheld (Thurstone and Jenkins, 1931). In order to establish beyond doubt that primogeniture is really a contributary cause of a condition, data would have to be collected to show that the children born after the patient were nearly always normal.

In the investigation described in this paper, an attempt was made to follow up, after a period of years, the families of undoubted cases of congenital pyloric stenosis. It was hoped, by this means, to obtain adequate data on which the influence of primogeniture might be accurately estimated. Unfortunately, the birth rate, during the period of the investigation, was declining and the following up of the families only discovered a very small number of brothers and sisters born after the patients. Nevertheless, the results of the investigation, though not absolutely conclusive, are of value in suggesting the probable aetiology of the condition.

The investigation was spread over a period of about five years. Most of the patients, who were the propositi of the study, had been treated in St. Thomas's Hospital, Great Ormond Street Hospital for Children, in London, England. The writers are indebted to a large number of helpers, among whom Miss D. E. Newlyn and Dr. D. M. Kapp should be specially mentioned.

Great difficulties were encountered in following up cases after long intervals. It was originally planned that the average interval between the operation and the visit to the family would be ten years: in fact the average interval was 6.66. The total number of propositi with unpublished pedigrees available for study was 434 but only 212 families were actually visited. Attempts made to visit the families of about 150 patients were unsuccessful. In rural districts, nearly all the families could be traced, but less than half of those who had lived in cities.

In the sibships of the 212 visited families (Series A), there were 221 affected children, of whom 185 were males, and 36 females. The diagnosis was confirmed at operation or autopsy in all cases except ten, eight males and two females, in whom the condition was medically treated. Of the children treated by operation, 130 males and 34 females were surviving at the time of the visit: five males had died of intercurrent diseases. In a number of the surviving cases, some abdominal disability remained, but the great majority appeared to be quite healthy. Of the ten medically treated cases, two males and two females died at the age of four months or under. The propositi, whose homes were not visited, (Series B), numbered 222 and in their sibships were altogether 228 affected children. Of these, 201 were males, 26 females, and one of unknown sex. In all, 386 out of 449 patients were males, i. e., 86.0.

THE GENERAL FEATURES OF THE VISITED FAMILIES (SERIES A)

In the 212 families, whose histories are summarized in the appendix, there were 528 children who were known to be either affected or unaffected (Table I). There were also 53 children, whose state with respect to the disease in question could not be ascertained: of these, 26 miscarried, 13 were stillborn or died at birth, and 14 died in infancy. The average number of children per family in the data is, therefore, less than three. The value of the data for deciding whether or not primogeniture is an aetiological factor depended a great deal on the number of normal or affected children born in the interval between the patient's operation and the visit. This number, 132, was disappointingly small. Some of the parents who were interviewed admitted that they had deliberately limited the family after

the patient's operation because of the fear that another child might have to undergo the same treatment.

The familial incidence of the condition is low but the disease is rare enough to make it likely that, if two affected children are found in the same sibship, this is not due to coincidence. In Series A, there were seven families with two children affected (See families Nos. 24, 68*, 119, 126, 167, 188 and 199*) and one family with three children affected (See No. 107). Further evidence of familial concentration was obtained by investigating near relatives. Two pairs of propositi were first cousins of one another (See Nos. 37 and 150, 148 and 164): four other patients each had a cousin affected (See Nos. 31, 63, 104 and 181). In addition to this definite familial incidence, there were doubtful histories of congenital pyloric stenosis in one mother, three brothers, one sister, one uncle and one cousin: for purposes of analysis these were counted as unaffected. In taking the family histories, attention was paid to the incidence of diseases of the alimentary tract, such as peptic ulcer, cholecystitis, peritonitis and cancer of the stomach. Four fathers and four mothers had definite histories of gastric or duodenal ulcer, there were also nine such histories among grandparents and four among patients' uncles. Appendicitis, peritonitis or ulcerative colitis were recorded in 13 parents, three sibs and five grandparents. Nine grandparents died of cancer in the alimentary tract.

TABLE I

SIBSHIPS (SERIES A) WHICH CONTAIN AT LEAST ONE CASE OF CONGENITAL PYLORIC STENOSIS: NUMBER OF CHILDREN

	Born before Propositus	Propositus	Twin of Propositus	Born after Propositus	Total
Affected Male	.....	178	2	5	185
Affected Female	.....	34	0	2	36
Unaffected Male	90	.....	1	73	164
Unaffected Female	88	.....	3	52	143
Total	178	212	6	132	528
(Miscarriages, Stillbirths, etc.)	(34)	(—)	(0)	(19)	(53)

There appears to be a slight tendency for patients to possess structural abnormalities other than pyloric stenosis: two patients (See Nos. 20 and 95) had hare lip and cleft palate, and in the family where three sibs were affected (No. 107), all three had abnormal conformation in the premaxillary region. One patient had a congenital heart lesion (No. 54) and one had club feet (No. 190). Mental disease was a rare complication; one subject was an idiot (No. 52), one was an imbecile (No. 104) and two were mentally retarded (Nos. 62 and 189).

Among the members of the families who were believed not to have congenital pyloric stenosis, there were seven cases of hare lip or cleft palate; one father (No. 7), three sibs (See Nos. 7, 74, and 162) and three other relatives. One brother had a congenital heart lesion (No. 90) and a sister in the same family had oesophageal stenosis. One sister (No. 162) had congenital absence of abdominal wall and another (No. 15) was simply stated to have been "deformed." A cousin (See No. 21) died of rectal atresia and another (See No. 168) had congenital intestinal

*In these families, the affected pair were twins, but whether monovular or binovular could not be ascertained.

obstruction. Some of these structural abnormalities may have a genetic relationship to congenital pyloric stenosis. The occurrence of blue sclerotics and brittle bones in patient and mother (No. 131) may have been quite unconnected with congenital pyloric stenosis. Very few cases of mental or nervous disease were found among near relatives.

The parents in four families (Nos. 12, 75, 129 and 134) were first cousins and in two families (Nos. 56 and 70) they were second cousins. There was an example also of a related case with first cousin parents in family No. 31. This incidence of first cousin marriages among parents of ascertained cases of congenital pyloric stenosis in Series A is significantly in excess of random expectation (Table II).

TABLE II

PARENTAL CONSANGUINITY

	Number with First Cousin Parents	Number with Second Cousin Parents	Total Number
Propositi and their Sibs (Series A).....	4	2	221
Other Relatives (Series A).....	1	0	4
Totals (Series A).....	5	2	225
Expected Totals with Standard Errors....	1.37±1.17	0.45±0.67	225
Propositi and Sibs (Series B).....	1	1	228
Totals (Series A and B).....	6	3	453
Expected Totals* with Standard Errors...	2.76±1.66	0.91±0.95	453

*A survey of 34,625 general hospital patients conducted by the Human Genetics Committee of the British Medical Research Council obtained the estimates 0.61% for first cousin parents and 0.20% for second cousin parents.

THE GENERAL FEATURES OF THE UNVISITED FAMILIES (SERIES B)

The 222 propositi in Series B provided some useful supplementary information, though in many aspects incomplete. In these sibships, 353 children were classified as affected or normal: there were also 16 stillborn sibs or miscarriages. Each propositus was, of necessity, the last to be born in the sibship. In six families, a sib was known to have been affected. Five patients had normal twin sibs. One patient suffered from hypospadias and left inguinal hernia in addition to pyloric stenosis and another suffered from achyluric jaundice. An unaffected sib of one propositus had a cleft palate and hare lip. Duodenal ulcer was diagnosed in the father of one patient.

The maternal grandmothers of one male patient were sisters and the parents of another were second cousins. The recorded incidence of consanguinity in the patients in Series B is thus not abnormal.

PRENATAL ENVIRONMENT

The examination of the effect of maternal age in cases of congenital abnormality sometimes reveals the presence of prenatal causes which would otherwise be unsuspected. The mean maternal age at birth for the 221 subjects with congenital pyloric stenosis in Series A was 28.77 years and for 220 subjects in Series B the mean was 27.73 (maternal age was unknown in eight instances in Series B). A reconstruction of the data in Series A, on the assumption that an affected person would be equally likely to occur at any of the maternal ages found in his sibship,

yielded the value of 28.06 years for the expected mean maternal age. The difference between the observed and the expected values are not significant and the result does not indicate that maternal age is an aetiological factor here. Paternal age was also found to be normal.

Of 221 cases in Series A, 109 were the results of first pregnancies. In Series B, 141 cases were first born, out of the total number 228. The large percentages of firstborn cases, 49.3 and 61.9 in A and B respectively, support the view that primogeniture is a significant aetiological factor. Caution is needed in accepting such a conclusion, however. In a recent survey of a very large series of births in Liverpool Maternity Hospital, Malpas (1937) showed that the expected proportion of first pregnancies was 46 per cent. It was admitted that the percentage might be unduly high because primiparae are more likely to be delivered in hospital than multiparae. The proportion of firstborn children in the general population depends upon the mean size of the family in the community and this is difficult to estimate. In particular, as Greenwood and Yule (1914) have shown, families selected by the presence of at least one affected member give an erroneous impression of the size of the family in the general population. The average size of sibships so selected tends to be too large. In a recent investigation of the families of mentally defective patients (Penrose, 1938), the number of births, including miscarriages, per sibship in the general community, estimated by the method of Greenwood and Yule, was 3.38. According to this estimate, the expected proportion of firstborn children should be one in 3.38 or 28 per cent: if this estimate is correct, the proportion of cases of congenital pyloric stenosis who are firstborn is significantly high. There are, however, two other factors which have to be considered. Congenital pyloric stenosis is a familial disease and it is one which may cause family limitation as soon as the occurrence of the first case in the family has been recognized. These two factors both tend to increase the proportion of firstborn affected children in the sample.

Suppose, for instance, that the normal number of children, born in a family in the general community, is s. Assume also that a certain congenital disease causes family limitation so that no children are born after the affected member. Let the true proportion of affected to total numbers of children, in families liable to the disease, be r. The proportion (p) of affected children who are first born in the family will be found to be

$$\frac{r}{1-(1-r)^s}$$

If, for example, a rare recessive condition causes family curtailment, the value of r is one quarter, p (the proportion of firstborn cases) has the value of 0.57 in a population where the normal sibship numbers two, a value of 0.43 where the normal sibship numbers three, and a value of 0.37 where the normal number is four children.

The mean size of family in the general population is not far above three and the known percentage of firstborn cases of congenital pyloric stenosis is about 0.50, this proportion would be of the right magnitude to agree with observation if the familial incidence (r) of congenital pyloric stenosis were about three-eighths. The evidence from the families investigated does not suggest that the manifest familial incidence can be nearly as high as this. By following up the 212 cases in Series A, who were the earliest affected in their sibships, 125 unaffected and seven affected children were ascertained (Table I). The propositi had four unaffected and two affected twin sibs. In Series B, there were five normal twin sibs of patients, 120 normal and six affected other sibs. It does not seem likely, therefore, that the manifest familial incidence can be far from one in twenty.

The ideal analysis of the comparative susceptibilities of the firstborn, second born, etc., to congenital pyloric stenosis could be carried out if all the families, in

which a case had occurred, were investigated about 20 years after the birth of the propositus. When the time interval between diagnosis and investigation is short, most of the cases are last born children and it is impossible, by the Yule-Greenwood method, to demonstrate any tendency for firstborn children to be affected. Instead of finding an excess of the observed number of affected firstborn over the expected number, when the interval is short, the method reveals a deficit. In the analysis of the present data, this deficit was seen unless the interval exceeded six years. In those families, which were investigated eight years or more after the birth of the propositus, there was a slight excess of the observed number of firstborn affected over expectation (Table III). The only way to obtain an idea of what the analysis would have revealed if the interval could have been longer was to extrapolate. This was feasible because the regression of size of family on length of interval since birth of affected child was found to be linear. If the average interval had been 10 years, the observed number of affected firstborn divided by the expected number of affected firstborn would have been 1.12. If the average interval had been 15 years, the ratio might have risen to 1.59 and, at 20 years, it might have risen to 4.45. Corresponding ratios were calculated for the second and third places in the

TABLE III

Number of Years Since Birth of Propositus	Number of Cases	Number of Cases which Result from First Pregnancies	
		Observed	Expected
0– 6	90	48	54.62
7	58	26	25.96
8–13	73	35	30.76
0–13	221	109	111.34

family and for the fourth to the ninth. In Table IV, the results of these calculations are shown. As no children are likely to be born more than 20 years after the birth of any propositus, the ratios in the bottom row of Table IV show the upper limit of the estimates for relative susceptibilities to congenital pyloric stenosis of children in the different birth ranks. The firstborn is perhaps about twice as likely to be affected as any child born afterwards, but is not more than six times as prone.

DISCUSSION ON THE MODE OF INHERITANCE

Two facts have been elicited by this enquiry. In the first place, there appears to be a definite familial incidence, which applies mainly to sibs and to cousins and which is small in magnitude. Secondly, the proportion of the patients with consanguinious parents exceeds random expectation. These facts taken together give reason for supposing that congenital pyloric stenosis is partly caused by a recessive Mendelian factor. Analysis of the data on the question of birth order is not conclusive but lends support to the assumption that the firstborn child is more likely to be affected than are the members of the sibship born later. Thus, the low familial incidence observed is not inconsistent with the hypothesis that the underlying causal factor is a recessive gene. A rare recessive trait should, indeed, be manifested in one quarter of the children in families which are prone to the disease. The observed familial incidence here, however, is only about one in twenty. If the firstborn were much more likely to be affected than other children, the familial

incidence would be much lower in large families than in small ones. This in fact, is the case in the present data. In Series A, apart from the two sets of affected twins, which are second born, in every family where more than one child is affected, one of them is firstborn. In the data of Series B, there are three instances of first and second, one of first and third, and one example of third and sixth children affected. The tendency to familial incidence is greatest at the beginning of the family. These considerations make it possible for a low familial incidence to be consistent with recessive diathesis as the underlying cause.

In the present data, as in previous work, a great excess of male over female patients is found: the males are about six times as numerous as the females. Among the unaffected sibs in Series A, however, the males exceeed the females, namely, 164 males to 144 females; in Series B there were 51 normal male sibs, 57 normal female sibs and 17 of unknown sex. Thus there were altogether 215 male and 201

TABLE IV

RATIOS OF OBSERVED TO EXPECTED NUMBER AFFECTED IN DIFFERENT BIRTH RANKS

The table is calculated upon the assumption that the increase of size of family with the lapse of time is linear.

Number of Years Since Birth of Propositus	Birth Rank		
	1st	2nd to 3rd	4th to 9th
0	0.82	1.17	6.19
5	0.93	0.96	1.72
6.66*	0.98	0.92	1.46
10	1.12	0.85	1.17
15	1.59	0.78	0.95
20	4.45	0.74	0.84

*Mean interval in the data.

female normal sibs. This distribution does not favor the assumption that the excess of male patients is due to the action of sex linked genes. Moreover, inspection of pedigrees shows that transmission to a male patient must frequently take place through the father. There is also no evidence of partial sex linkage. It seems correct to assume that the male constitution has less resistance than the female constitution to the development of the disease. This explanation of the differential sex incidence helps to account for the low familial incidence observed.

On the hypothesis that a rare recessive gene is the underlying cause, the chance that any child is susceptible in a sibship, where the disease can occur, is usually one in four. If the degree of susceptibility of the firstborn male child is maximal, the chance of its being affected is one in four. The degree of susceptibility of a firstborn female or of a male not firstborn will be much less than this, and the female who is not firstborn stands very little chance of being affected. The manifest familial incidence of the disease in a family of three children, which mainly depends upon the chance of the occurrence of an affected firstborn male, will have a value not much greater than $\frac{1}{4}$ times the chance of being a male times the chance of being firstborn, i. e., $\frac{1}{4} \times \frac{1}{2} \times \frac{1}{3}$ or $\frac{1}{24}$. The observed familial incidence of $\frac{1}{20}$ is thus not in disagreement with the view that the predisposition has a familial incidence of $\frac{1}{4}$. The gene, moreover, must be commoner than the frequency of the disease in the general population would at first suggest. Hence, it is not unlikely that occasionally parent and child would both be affected.

The hypothesis that a recessive gene, whose manifestation is influenced by birth order and sex, is the cause of congenital pyloric stenosis can be used to interpret the presence, in certain families, of abortive cases and associated abnormalities. Some structural abnormalities found in patients may have been accidentally present, but others, like hare lip, cleft palate and intestinal atresia, may have been modified manifestations of the same underlying gene. It is conceivable, also, that some of the alimentary diseases in relatives may have been manifestations of the gene in the heterozygous form. Peptic ulcer, for example, like congenital pyloric stenosis, is more often found in males than in females and has been believed to be due to an irregularly dominant genetic factor (Levin and Kucher, 1934). In homozygous form, this factor might affect the same organ more severely and earlier in life. In support of this view, it may be recalled that ulcers of the duodenum associated with pyloric stenosis in infants have been recorded by several observers (Holt, 1913; Harrison, 1931).

SUMMARY

The families of 212 cases of congenital pyloric stenosis were investigated about 6½ years after the births of the propositi. In this way, nine more cases were discovered in the sibships, two of whom were twins of the propositi. The data were amplified by reference to 222 propositi whose families were not visited. The data are consistent with the hypothesis that the disease is a recessive diathesis. Males are more susceptible than females and the firstborn child is more susceptible than children born afterwards in the same sibship. The relationship of congenital pyloric stenosis to some other diseases is discussed.

APPENDIX

DETAILS OF 212 SIBSHIPS: SERIES A

N—Identification number of sibship.
A—Number of years between birth of first affected child and date of investigation.
B—Excess of father's age over mother's age.
C—Order of birth in sibship. The sex and maternal age at birth of each sib is shown in the appropriate birth rank. Affected children, who were living at the time of investigation, are indicated by underlining once. Affected children, who did not survive, are marked by double underlining.
All cases were surgically treated, except those marked thus: *.
Additional notes on the sibships can be found by reference to the identification numbers.

N	A	B	C 1	2	3	4	5	6	7	8	9	10
1	2	1	F 30									
2	5	5	F 21	F ..	M25	M27	M29	M30	M33			
3	1	2	....	M31								
4	6	2	M24									
5	3	0	M19	M22								
6	5	2	M22									
7	7	1	M25	M27	F 31	M33						
8	2	1	M28	M35								
9	2	?	F 23									
10	4	4	F 23	M24	F 27							
11	9	0	F 21	F 23	M27							
12	5	2	M27									
13	5	10	F 23	M27								
14	2	0	F 18									

N	A	B	C 1	2	3	4	5	6	7	8	9	10
15	2	—1	F . .	F 27	M30 F 30							
16	11	0	M. .	M39								
17	4	0	M17	M19	F 24	M26	. . . .	F 28	F 31	M33		
18	13	10	M19	F 22	M23	F 25	F 26	F 29	F 31	F 33		
19	2	6	M29	. . . .								
20	0	7	M28									
21	2	1	M38									
22	9	0	. . . .	F 29	M30							
23	5	0	M27	F 30								
24	5	0	M20	M22								
25	5	—2	M29	M32	F 41							
26	4	2	M23	M25								
27	4	5	F 32	M34								
28	9	1	F . .	M33								
29	1	0	M29									
30	4	1	M29	M35								
31	1	3	M27									
32	10	—3	F . .	. . . .	M29	M35						
33	7	6	M22									
34	10	4	M23	F 24	M26	M33						
35	1	6	M29									
36	10	10	F 32	M33	M38							
37	2	7	M26	F 30	M39							
38	3	2	F 22	M25	M27							
39	2	—3	M28	M32	F 34	M35	M37	F 42	M44			
40	7	2	M38									
41	8	—1	F 25	M26	F 29	M31	M32	F 38				
42	8	5	M22	F 24	M27	F 31						
43	11	10	M22	F 24	M26	M28	M30	M34	M37			
44	5	4	F 29	M33								
45	3	3	M25									
46	3	2	M25									
47	12	12	F 29	F 32								
48	6	8	M22	F 24								
49	4	1	M26									
50	4	2	M22									
51	5	7	M21	25								
52	3	3	M29									
53	9	—1	M27	M32								
54	3	1	M25									
55	8	—1	M24	M27								
56	5	—1	F 25	M29								
57	8	—3	M33	M36								
58	10	10	M25									
59	8	5	F 28	F 31								
60	6	3	M24	F 27	M31							
61	6	10	F 41									
62	7	6	M34									
63	6	4	F 26	F . .	F 29							
64	7	—2	F 29									

N	A	B	C 1	2	3	4	5	6	7	8	9	10
65	6	0	F ..	M21	M25							
66	7	—6	M28	F 29	M31	F 35						
67	7	—?	M29	M31								
68	7	1	M21	M22 M22								
69	6	17	F 28									
70	7	1	F 29	M33	M35							
71	7	19	M28	M29	M32							
72	2	0	M28									
73	8	5	F 31									
74	6	7	M22	F 25								
75	7	1	M27	M28	M32							
76	6	10	F 34	M36	F 38	M43						
77	7	1	M26	M28	M31							
78	6	5	F 24	F 26	F ..	M29	M30					
79	8	2	F 26	M29								
80	8	3	M22	F 24								
81	8	1	M23									
82	7	1	F 19	F 22	M28	M34						
83	8	1	F 20	F 26	F 27	M29	F 31	M35	M37	M38	M40	....
84	7	2	M30	M33	M37							
85	9	3	M21	F 23	M27	M30						
86	7	0	....	M31	F ..	M38						
87	8	4	M28	F 29	F 32							
88	7	3	M23	M28	....							
89	7	2	M23	F 27								
90	7	0	M.. F 29	M34	....							
91	7	5	F 34	M36	M..							
92	7	9	M19	F 25								
93	7	—1	M26	M28								
94	6	7	F 32	F 33	M34	M39						
95	8	—3	M33	....	M38	M39						
96	6	0	F 23	M29	F 32	F 37						
97	6	5	F 17	M19	M24	M27						
98	6	1	M31									
99	7	—4	M33	M34	....							
100	6	0	M21	F 24								
101	7	2	M21	M25	M29							
102	7	3	F 22	F 27	F 29							
103	6	3	M25									
104	7	2	F 24	F 25	....	F 33						
105	6	10	F 23	F 28								
106	7	7	F 25	M26	F 29	F 31	M33					
107	10	4	F 24	....	M27	F 29	....					
108	7	—2	M38	....								
109	7	—4	F ..	....	M36							
110	7	1	F 30	M32								

N	A	B	C 1	2	3	4	5	6	7	8	9	10
111	6	—2	M32									
112	7	2	....	M35	F 39							
113	6	7	F 32	F 34								
114	6	0	M40	F 44								
115	6	1	F 26	M30								
116	5	1	M27									
117	7	9	F 23	F 24	F 27	M29	F 34					
118	7	2	M21	M23	F 25	F 29						
119	7	1	M22	M23	M26							
120	8	0	F 25	M27								
121	8	—6	M31									
122	6	0	M24	M27								
123	7	—1	F 23	F 26								
124	7	0	F 31	M38	F 40							
125	7	0	M20	F 26	F 29	M30	M32					
126	8	6	M23	M24	M26							
127	7	20	M39	F ..	.... /							
128	10	—2	M28									
129	7	5	M22									
130	10	—3	M33									
131	7	12	....	F 38								
132	10	0	F 25	M27								
133	8	—2	....	F 34	F 38							
134	10	0	F 33	M34	F 38							
135	10	—3	F 24	....	M31							
136	7	0	M28									
137	7	0	M23	F 26								
138	7	7	M29	M31								
139	7	—6	M32	F 34	F 36	....	F 39	M41				
140	10	0	M23									
141	7	1	F 24	M26								
142	7	1	M28	M31	F 38							
143	7	4	M31	M37								
144	7	—3	M26	M27								
145	10	2	M19	M26								
146	10	3	M23	F 24	M26	M28	F 30	M32	M34	M35	M38	
147	6	—2	M30									
148	4	—1	M23	M27								
149	5	4	M25									
150	7	3	M34									
151	8	3	F 25	F 27	M33							
152	7	1	M23	M25	M27	M30						
153	8	4	M25	M28	M31							
154	9	1	M23	M26	M28	M31	M34	....	M37			
155	5	5	M21	M27								
156	6	3	M19	....								
157	7	—1	M24	F 30								

N	A	B	C 1	2	3	4	5	6	7	8	9	10
158	8	0	M23	M25	M27	F 29	M31	M32	F 34	....		
159	5	8	M21	M30	M31							
160	7	—5	M30	F 31	M34	M37						
161	8	6	M22	F 29								
162	6	4	....	F ..	M28	M31						
163	8	1	M23	M25	M33							
164	7	0	M24	M30								
165	8	—1	M30	F 32	F ..	F 36	M38	F 40				
166	6	13	M20	F 22	F 23	F 27	....	M34	M37			
167	13	2	M32	F 33	....							
168	10	4	M24	M27								
169	?	?	....	M34								
170	6	3	M23	M25								
171	4	8	M18									
172	4	1	M25	F 26	M30	M35						
173	4	3	F 28	M32								
174	4	6	M22	F 26								
175	11	0	M25	M27	M28	M29	....					
176	4	3	M16	F 18								
177	6	6	M25	M27								
178	6	2	M26									
179	7	1	F 31	F 35								
180	11	—1	F 22	M24	F 25	M28	F 30					
181	8	—2	F 28	M30	M39							
182	11	—7	M41	....								
183	9	23	M22	M.. / M..	M24	M26	F 28	M33				
184	8	—1	M29	M35								
185	11	4	M26 / F26	F 29	M33 / F 33							
186	8	0	F 19	F 22	M24	M27	F 29	F 32	F 34	F 36		
187	8	4	M17 / F 17	M19								
188	13	4	M19	F 23	M27	M29						
189	10	3	M21									
190	6	1	M22									
191	9	—8	M37									
192	3	7	M23	M24	M26	F 28	F 33	M35				
193	7	—1	M28									
194	8	—5	M33	F 34								
195	11	—2	M31	F 33								
196	2	5	M22									
197	5	8	M21	M22								
198	9	4	F 20	M22	M25	M29						
199	7	3	F ..	M28 / M28	F 34							
200	11	1	M..	M26	F 27							
201	4	3	M20	M22	M26	M34						
202	6	1	M27 / M27									

N	A	B	C 1	2	3	4	5	6	7	8	9	10
203	2	2	F 30	M35*								
204	1	1	F 22	M33*								
205	1	—2	M28*									
206	2	7	M25	....	....	M28*	F 29					
207	8	2	M25*									
208	9	1	M24*	F 27								
209	6	1	F 28*	M29								
210	9	4	M25	M26*	M28	M30						
211	10	1	F 35*	M37								
212	10	0	M22*	M23	F 25							

NOTES

2. C2—died at birth. Two sisters of mother—cleft palates.
3. C1—miscarriage at 4 months.
5. C1—died of measles at 10 months. Mother's cousin—Little's disease.
7. Father—cleft palate. C1—double hare lip.
9. Mother—history of vomiting in early infancy.
12. Father and mother—first cousins.
15. C1—stillborn, "deformed." C2—one twin died at one year of diarrhoea and vomiting.
16. C1—stillborn.
17. C5—miscarriage at 3½ months.
19. Mother—appendectomy at 19. C1—died at 7 weeks. C2—miscarriage at 1 month.
20. C1—hare lip and cleft palate, died at 4 weeks.
21. Mother's sister's son died at 1 week of atresia of rectum.
22. C1—miscarriage at 2 months.
27. Mother's mother—haemorrhage due to gastric ulcer.
28. Father—died at age of 40 of ulcerative colitis. C1—died at 1 day.
30. Father—appendectomy at 32. Mother—appendectomy at 31. C2—undescended testis.
31. Two children of 2 sibs of one of the father's grandparents were the parents of a male who was medically treated for pyloric stenosis.
32. C1—stillborn. C2—miscarriage at 3 months. Father's mother—died of cancer of the stomach.
36. C2—infantile paralysis at 14 months. C3—hemiplegic, but no history of febrile attack.
37. Father's sister's son—No. 150, C1.
38. Mother's mother—cholecystectomy.
39. Father's sister—cholecystectomy.
40. Mother—gross rachitic deformity. C1—born by caesarean section.
41. C1, C2, and C6—died of measles in infancy.
42. Mother's brother's son—medically treated for severe vomiting at 3 months.
45. Father—appendectomy at 28. Father's brother—died of cancer of the stomach.
46. Mother's brother—medically treated for severe vomiting in infancy.
49. Father—abdominal tuberculosis. Father's mother's father—died of cancer of rectum two children of his sibs died of cancer of stomach.
51. Father—pulmonary tuberculosis.
52. C1—idiot with small head.
54. C1—congenital heart lesion.
55. Father's father—died of cancer of stomach.
56. Father's mother and mother's father—first cousins. Father—duodenal ulcer; appendicectomy at 32. Father's mother—perforated gastric ulcer.
58. C1—hydrocoele at 2 years. Father's father—died of cancer of the oesophagus.
60. Mother—slight exophthalmic goitre.
61. Mother—duodenal ulcer at 42.
62. C1—mentally retarded.
63. C2—died at 2 months. Father's brother's son—treated medically for pyloric stenosis.
64. Mother—slight goitre.
65. C1—stillborn.
68. C2—both twins died at about 2 months.
70. Father's father and mother's father—first cousins. Mother—appendicectomy at 39.
71. C1—died at 10 weeks.
74. C2—hare lip. Father's father—gastrectomy for ulcer.
75. Father's father and mother's father—brothers. C1—died at 10 weeks. C2—recurrent vomiting from 2 to 5 years.

76. C2—died at 8 weeks.
77. C1—died of diphtheria at 5.
78. C3—"died at birth."
81. C1—died at 9 weeks.
82. C3—died of diphtheria at 4.
83. C2—appendicectomy at 14. C8—pulmonary tuberculosis. C4 and C5—died of diphtheria in childhood. C1—miscarriage. Father's father—died of cancer of the bowel. Mother's sister—cancer of the stomach.
84. C2—died at 8 weeks.
85. C1—died at 7 weeks.
86. C1—died at 2 months. C2—appendicectomy at 11. C3—died at 4 months of gastro-enteritis.
87. C1—died at 8 weeks.
88. C3—stillborn.
89. C1—died at 11 weeks.
90. C1—male twin died at 6 weeks of congenital heart. C2—died at 2 months. C3—died at 3 days of oesophageal stenosis.
91. C2—died at 13 weeks. C3—died at one month.
93. Mother—dyspeptic. C1—died at 8 weeks. Mother's brother—two operations for gastric ulcer.
95. C1—hare lip and cleft palate, died at 11 weeks. C2—stillborn.
97. Father—dyspeptic.
98. Father had attacks of abdominal pain.
99. C2—appendicectomy at 2 years. C3—induced abortion. Mother's sister—appendicectomy.
100. Father—appendicectomy at 23 years.
101. C3—hernia.
103. Mother—appendicectomy at 30. Mother's brother—appendicectomy.
104. C3—miscarriage. C4—imbecile with subthyroidism. Father's brother's son—congenital pyloric stenosis.
105. Father—duodenal ulcer at 40; perforated gastric ulcer at 43. Mother's brother—died of peritonitis.
106. C2—died of lymphosarcoma of thymus at 11. C5—died at 8 weeks.
107. Mother—appendicectomy at 30. C2—miscarriage at 3½ months. C5—miscarriage at 5½ months. C1, C3, and C4—very slight degree of cleft palate in each case. Father's father—died of cancer of stomach.
108. C2—miscarriage at 4½ months.
109. C1—died in convulsions at 4 days. C2—miscarriage at 3 months. Mother's mother—cholecystitis.
110. Mother—duodenal ulcer at 36.
111. Two of mother's nephews—appendicectomy.
112. C1—miscarriage. C2—died at 15 weeks. Mother's mother—died of cancer of stomach.
113. Mother—appendicectomy at 28; probably also gastric ulcer. Father's father—died of carcinoma of colon.
114. Father—chronic colitis. C1—died at 8 weeks. Mother's mother—died of cancer of stomach.
118. Mother—gastric ulcer at 16. C2—died at 9 months. C3—epileptic.
119. Father's mother—cholelithiasis. Father's mother's brother—hare lip.
120. Mother—umbilical fistula.
122. Mother's mother—gastric ulcer.
124. Father—appendicectomy at 40. C2—died at 7 weeks.
125. C4—died at about 2 months.
126. C1—died at 6 weeks. Father's brother—cancer of stomach. Mother's mother—duodenal ulcer.
127. C1—died at 6 weeks. C2—stillborn. C3—miscarriages. Mother's sister's daughter—died of appendicitis at 11.
129. Father's mother and mother's mother—sisters.
130. Mother's sister—gastric ulcer at 30.
131. Mother—bluish sclerotics: one tibia curved. C1—miscarriage. C2—blue sclerotics and brittle bones.
134. C2—died of diphtheria at 3½. Father's father and mother's father—brothers.
135. C2—stillborn. C3—died at 6 weeks.
136. C1—died at 9 weeks.
137. Father's sister—died of peritonitis at 17.
138. Mother's mother—died of subphrenic abscess.
139. C4—stillborn. C6—died at 13 weeks.
140. C1—died at 5 weeks.
141. C2—died at 10 weeks.

143. C1—died at 9 weeks.
145. Father's brother's son—peritonitis. Mother's brother—died of intussusception at 4.
146. C7—died at 6 months.
148. Father's sister's son—No. 164, C2. Mother's mother—gastric ulcer at 47.
149. C1—died at 11 weeks.
150. Mother's brother's son—No. 37, C3.
154. C3—died at 3 months. C6—miscarriage.
156. C1—died at 8 weeks. C2—miscarriage.
158. C8—miscarriage at 6 weeks. Father's mother—died of cancer of bowel.
159. C2—died at 4 weeks.
162. Father—pyloric ulcer at 32. C1—miscarriage. C2—abdominal wall malformed, died at 3 weeks. C4—abortive hare lip and cleft palate.
164. Mother's brother's son—No. 148, C1.
165. C3—stillborn.
166. C5—miscarriage.
167. C3—stillborn. Father's sister—appendicectomy.
168. Mother—appendicectomy at 14. Father's nephew or niece (whose parents were first cousins)—died of congenital intestinal constriction.
169. Mother—duodenal ulcer. C1—miscarriage. Mother's father—died at 67 of gastric ulcer.
170. Mother—hyperemesis gravidarum ar 24. C2—died at 4 weeks.
172. C4—died at 3 weeks.
175. C5—miscarriage.
176. C1—died at 4 months.
177. Father—exophthalmic goitre at 22. Father's brother—gastric ulcer.
178. C1—died at 9 weeks.
179. C1—died at 6 weeks.
180. C4—died of meningitis at 9 months. Mother's father—died of perforated ulcer in alimentary tract. Mother's mother—gastric ulcer. Mother's brother—duodenal ulcer.
181. Mother—goitre. Mother's brother's daughter—pyloric stenosis, medically treated. Mother's father—died of duodenal ulcer.
182. C1—died at 7 weeks. C2—miscarriage.
183. C2—one twin died at 2 months, the other at 2 days.
184. C1—hernia.
185. C1—died at 7 weeks.
186. Father—severe dyspepsia.
187. Mother's father—gastric ulcer.
188. C4—hernia.
189. C1—mentally dull.
190. C1—talipes.
192. C3—tuberculous peritonitis.
197. C1—died at 9 weeks.
198. C1—died at 9 weeks.
199. C1—died at 3 days. Father's sister—dyspeptic.
200. C1—died of wasting disease at 3.
201. C4—died at 10 weeks.
206. C2—miscarriage at 3 months. C3—miscarriage at 1 month.
209. C1—died at 4 months.
210. C2—died at 7 weeks.
211. C1—died at 3 months.
212. C1—died at 7 weeks.

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